



Expert Report of Samuel M. Cohen, M.D., Ph.D.

Regarding Angela Swartz and Teddy Swartz v. E. I. du Pont de Nemours and Company

May 30, 2019

I. Personal Background

I am a professor at the University of Nebraska Medical Center. Details of my personal background and expertise are provided in my report of September 16, 2016 and in the attached curriculum vita. I will only mention a few updates here. I continue to be active as a surgical pathologist and active in research and active on expert panels in addition to teaching. I have received additional awards in recognition of my expertise and accomplishments, including the Distinguished Scientist Award from the American College of Toxicology (2016) and the Merit Award from the Society of Toxicology (2017). In addition to other activities, I serve on the US Environmental Protection Agency (EPA) Science Advisory Board (SAB).

II. Summary of Work and Principal Opinions

I have been requested to review the medical records and other information relating to Angela R. Swartz, to evaluate the amount of increased risk of kidney cancer that she had from various risk factors, and to respond to the relevant portions of the expert report concerning Mrs. Swartz submitted by Dr. Vitaly Margulis. All of my opinions are stated to a reasonable degree of scientific and medical certainty.

I have been instructed to assume that C8 is capable of causing kidney cancer in humans, including the plaintiff, and I have accepted this instruction. I have been asked to compare the amount of increased risk of kidney cancer that Mrs. Swartz had from various other risk factors with the amount of increased risk for kidney cancer that she had from her exposure to C8. In summary, Mrs. Swartz had approximately a two-fold or more increased risk of developing kidney cancer due to her long-standing obesity and also approximately a two-fold increased risk of developing kidney cancer due to her long-standing history of hypertension. Based on the relatively low levels to which she was exposed to C8 and her measured blood level of C8 and comparing her substantial increased risk of kidney cancer posed by her obesity and hypertension, it is my opinion that she would have developed kidney cancer even if she was not exposed to C8.

The contribution of heredity to her risk of developing kidney cancer is unknown, since she does not know her father or any of his family's history regarding kidney cancer, so that risk factor cannot be excluded. She is a non-smoker, but there was likely a small increased risk for her developing kidney cancer from her exposure to second hand smoke growing up and from her husband and sister, although this amount of increased risk was likely to have been considerably less than her increased risk from obesity and hypertension.

III. Mrs. Swartz's History

Mrs. Swartz is a Caucasian female born July 2, 1961. She lived in Mason, West Virginia 1961-1979, Letart, West Virginia 1979-1996, and Gallipolis, Ohio 1996 to the present. She stated that she drank public water from 1961 to 1996 while in West Virginia, but drank bottled water at home from 1996 to present. She claims exposure to drinking water containing at least 0.05 ppb of C8 while (1) working part-time (about 23 hours a week) at Big Ben Food Land grocery store in Pomeroy, Ohio for about 16 months, starting in May 1992 and ending in October 1993; (2) visiting her mother, who lived in a house served by the Pomeroy water district in 1990-1992; and (3) visiting her sister, who lived in a trailer served

by the Toppers Plains-Chester Water District from 1988 to the present. Her blood level of C8 in March 2006 was 16.5 ng/ml.

Mrs. Swartz presented to her doctor with a complaint of hematuria on December 27, 2016, which led to a diagnosis of a small tumor in her right kidney that was excised by a robotic assisted laparoscopic partial nephrectomy on March 14, 2017. The tumor was diagnosed as a clear cell renal cell carcinoma, the most common type of kidney tumor, and was classified as grade 2, and was 2 cm. in greatest diameter which makes it stage 1a. It was indicated in the pathology report that there was no extension outside of the kidney and no invasion of the renal vein or kidney pelvis. However, it was indicated that the tumor might microscopically be at the resection margin, although the urologist later restated his conclusion that clear margins were achieved. Based on my review of the pathology, I agree with the pathologist that the tumor microscopically appears to abut the resection margin. However, it is unlikely that there was any residual tumor remaining as it appeared to be right at the margin and any residual tumor cells would have been destroyed by the inflammatory reaction that occurred as a consequence of the healing of her kidney following the resection. Moreover, as stated by the urologist, no residual tumor being present is further supported by the fact that there has been no recurrence of cancer in over two years since the resection. She had no prior history of renal disease, with her serum BUN and creatinine within the normal range, and she shows no evidence of decreased renal function since the surgery.

She had a longstanding history of obesity with her BMI usually in the range of 35 to 40, and occasionally greater than 40, which is defined as morbid obesity. She also had a long history of hypertension, for which she received treatment. She also had histories of hypothyroidism and hypercholesterolemia for which she received treatment.

IV. Materials Reviewed

To reach my opinions in this matter, I have reviewed an extensive amount of material. Various specific references and materials are listed at the end of this report, and my general knowledge of the fields of pathology, toxicology, carcinogenesis and evaluating the likelihood of harm have been utilized in this evaluation, including all of the articles and chapters listed in my CV and the articles cited in those publications.

I have also reviewed the medical files of Mrs. Swartz, the deposition transcripts and expert reports identified at the end of this report, and other materials listed at the end of this report.

V. Kidney Cancer and Mrs. Swartz

Renal cell carcinomas commonly occur in the general United States population, and account for approximately 2-3% of adult malignancies. They comprise the vast majority of kidney tumors in adults, estimated at 80-85% of all kidney tumors (Murphy et al., 2004; Hakimi et al., 2013). In the United States, it is estimated that there are about 35,000 new cases of renal cell carcinoma per year and approximately 12,500 deaths each year. Men are generally affected more commonly than women, in an approximate ratio of 3 to 2. Renal cell carcinomas can occur at any age, but the incidence increases with age, and they are usually detected after the age of 40. The reported incidence of renal cell carcinomas has been increasing in the United States over the past two decades, and this has been primarily due to the increased detection of small, low grade tumors (Hollingsworth et al., 2006; Murphy et al., 2004), and also likely

secondary to the increasing incidence and severity of obesity (Hakimi et al., 2013; Renahan et al., 2008; Chow et al., 2010; MacLeod et al., 2013; Kendall et al., 2015; Lauby-Secretan et al., 2016). Small tumors are frequently detected incidentally during imaging studies in patients being evaluated for some other disease or medical issue. The newer imaging technologies, especially CT and MRI scans, are able to detect small kidney masses that could not be easily detected with standard x-rays (Jayson and Sanders, 1998; Hollingsworth et al., 2006).

There are several types of renal cell carcinoma, but the most common is classified as clear cell renal cell carcinoma based on the clear appearance of the tumor cells in histopathologic sections (Murphy et al., 2004). This sub-type is the most common form of kidney cancer, and accounts for approximately 70% of renal cell carcinomas. Another subtype of renal cell carcinoma, accounting for approximately 5% of renal cell carcinomas, is the chromophobe carcinoma, classified based on its histopathologic appearance, which is distinct from clear cell carcinomas. There are several other types of renal cell carcinoma with distinctive histopathologic, cytogenetic and molecular characteristics (Murphy et al., 2004; Jonasch et al., 2012). In addition, there are several uncommon tumors in the kidney that are not included as renal cell carcinomas, such as urothelial cell carcinomas of the kidney pelvis and various non-epithelial tumors (Murphy et al., 2004).

For renal cell carcinoma there are known genetic and environmental factors that contribute to its causation (Murphy et al., 2004; Jonasch et al., 2012; Hakimi et al., 2013). Several genetic disorders, such as von Hippel-Lindau disease, are associated with the development of renal cell carcinomas. Birt-Hogg-Dube is a syndrome with an increased risk of kidney tumors, most often chromophobe renal cell carcinomas, oncocytomas, or tumors that are a mixture of these two types (Cohen and Zhou, 2005). Several genes have been identified that appear to be associated with the development of renal cell carcinoma, including the von Hippel-Lindau gene (VHL), fumarate hydrase (FH), and the folliculin gene (FLCN) (in Birt-Hogg-Dube syndrome) (Jonasch et al., 2012).

Various environmental factors have also been identified as causal risk factors and associated with an increased risk of renal cell carcinoma, including obesity, hypertension, and cigarette smoking (Murphy et al., 2004; Hakimi et al., 2013; McCredie and Stewart, 1992; Adams et al., 2008; Macleod et al., 2013; Chow et al., 2010; Colt et al., 2011; Dobbins et al., 2013; Calle and Kaaks, 2004; Flaherty et al., 2005; Roberts et al., 2010; Lipworth et al., 2006; Kendall et al., 2015; Lauby-Secretan et al., 2016; World Cancer Research Fund and American Institute for Cancer Research, 2018). Some studies have suggested a relationship with diabetes mellitus, but more specific investigations indicate that this is likely related to the commonly co-associated factors of obesity and hypertension (Macleod et al., 2013; Murphy et al., 2014).

Obesity is well-established as a major causal risk factor for the development of renal cell carcinoma. Some studies indicate that overall, approximately 40% of renal cell carcinomas can be attributed to obesity (Hakimi et al., 2013; McCredie and Stewart, 1992; Flaherty et al., 2005; Renahan et al., 2008; Adams et al., 2008; Chow et al., 2010; MacLeod et al., 2013; Kendall et al., 2015; Pisichon et al., 2006; Lauby-Secretan et al., 2016). Studies have shown that the risk of kidney cancer increases with the severity of the obesity, with an overall increased risk of about two-fold compared to non-obese individuals. There is considerable evidence that the risk increases with increasing level of BMI. It is estimated that those in the highest 5% by body mass index (BMI) have approximately a five-fold higher

risk than an individual with a normal BMI (Murphy et al., 2004). Some studies have reported that individuals with morbid obesity ($BMI \geq 40$), have an attributable risk for developing renal cell carcinoma of 60-90%, with risk increasing by about 30% per 5 BMI units above normal (Hakimi et al., 2013; Renehan et al., 2008; Chow et al., 2010). In a very large cohort study in Norway (Bjorge et al., 2004) involving two million individuals, the relative risk of renal cell carcinoma increased by 1.05 (confidence interval, 1.04 to 1.06) per BMI unit above the normal range (a 4% increase per BMI unit). This included individuals that were overweight and obese. A similar relative risk was calculated based on an extensive meta-analysis (relative risk of 1.07, confidence interval of 1.05-1.09) (Bergstrom et al., 2001). Mrs. Swartz has had a BMI usually in the range of 35-40 for many years, occasionally over 40. Given that the overall risk for obese individuals is about two-fold, and that individuals with higher BMI have a higher risk, Mrs. Swartz had at least a two-fold increased risk of kidney cancer compared to individuals with a BMI less than 25.

Hypertension is also a well-established causal risk factor for renal cell carcinoma (Lipworth et al., 2006; Lindblad, 2004; Flaherty et al., 2005; McCredie and Stewart, 1992; Yuan et al., 1998; Shapiro et al., 1999; Colt et al., 2011). The overall risk of kidney cancer is increased approximately two-fold, but the specific quantitative relationship to various blood pressure levels is difficult to ascertain because of the variability in measurements during the day and the fact that many patients with hypertension receive medical treatment for it. There has been some evidence that some of the increased risk associated with hypertension could be related to use of anti-hypertensive drugs. Hypertension affects the kidney and is known to produce damage to the kidney in ways that could lead to increased cell proliferation and an increased risk of renal cell carcinoma. Overall, the evidence supports an increased risk of renal cell carcinoma by hypertension, independent of the drugs used to treat it. In the Campbell-Walsh text on Urology, the leading textbook on Urology, hypertension is listed as an etiologic factor for renal cell carcinoma (Wein et al., 2011). In a leading textbook of urologic pathology (MacLennan and Cheng, 2008), they also state that “the bulk of epidemiologic evidence implicates it as a causal risk factor”. Based on her long-standing history of hypertension, even requiring treatment, it can be estimated that Mrs. Swartz had approximately a two-fold increased risk of kidney cancer compared to non-hypertensive people.

Cigarette smoking is also a causal risk factor for renal cell carcinoma (Murphy et al., 2004; Hakimi et al., 2013; Adams et al., 2008; MacLeod et al., 2013; Chow et al., 2010; Dobbins et al., 2013; Calle and Kaaks, 2004; Roberts et al., 2010). Although not specifically addressed for renal cell carcinoma, it is likely that second hand smoke is a risk factor for kidney cancer, as it is for the other adverse effects related to cigarette smoking (Surgeon General, 2014). Mrs. Swartz indicated that she has never been a cigarette smoker herself, but she has lived with individuals that smoked most of her life. She claims that although they smoked in houses and vehicles that she frequented, they did not smoke directly in her presence, and if true, that would reduce the amount of her increased risk. Although some increased risk from second hand smoke cannot be excluded for Mrs. Swartz, it is likely that any increased risk would have been insignificant compared to her increased risk from obesity and hypertension. Scientific study continues as to whether other chemical exposures such as trichloroethylene are linked with increased kidney cancer risk.

Kidney cancer, like other cancers, also frequently arises spontaneously due to the spontaneous errors that occur in the DNA during normal cell replication (Cohen and Ellwein, 1990; Moolgavkar and Knudson, 1981; Tomasetti and Vogelstein, 2015).

For clinical management purposes and prognosis, renal cell carcinomas are evaluated on the basis of grade and stage at the time the patient is diagnosed (Murphy et al., 2004; Chin et al., 2006). Grade refers to the degree of differentiation of the tumor (how closely it resembles normal), with a 4 grade system most commonly used (referred to as the Fuhrman grade). Grade 1 is the most well differentiated and the least aggressive grade. It is associated with an excellent prognosis, relatively small tumors (<4 cm.), and is usually treated only with surgery, especially if the tumor is confined within the kidney. Grade 4 is the most poorly differentiated and grades 2 and 3 are intermediate. Stage refers to the extent of the disease. Stage I includes tumors that are 7 cm. in greatest dimension or less and are confined to the kidney. Stage II includes tumors that are more than 7 cm. in greatest dimension but are still confined to the kidney. Stage III refers to tumors that have spread outside the kidney locally or have spread to lymph nodes. Stage IV includes tumors that have spread to distant tissues such as lung, bone, or elsewhere. Mrs. Swartz had a small renal cell carcinoma (2 cm.) and it was low grade (Grade 2). Given the small size, low grade and low stage (Stage 1a), Mrs. Swartz's prognosis is excellent.

VI. Overall Evaluation of Mrs. Swartz

Mrs. Swartz was 56 years old when she was diagnosed with a grade 2, 2 cm, Stage 1a clear cell renal cell carcinoma treated in March 2017 with a laparoscopic partial nephrectomy. She had no evidence of abnormal renal function, with her serum BUN and creatinine in the normal range, which continues to the present. Her family history is unclear, since her father is unknown. Although there is no indication of a hereditary basis for her renal cell carcinoma, that risk factor cannot be excluded. She had two very significant risk factors for renal cell carcinoma, long standing obesity and hypertension. Her obesity has occasionally been in the morbid range (BMI greater than 40). Although the overall increased risk for obesity for renal cell carcinoma is approximately two-fold, individuals with morbid obesity generally have higher risks, up to five-fold. Based on her history, Mrs. Swartz had at least a two-fold increased risk of developing renal cell carcinoma compared to an individual with BMI <25. Her hypertension also gave her a substantial increased risk of developing renal cell carcinoma of approximately two-fold. Although she is not a cigarette smoker, she has lived with smokers most of her life. Second hand smoke cannot be excluded as contributing to her risk, but the increase in risk is likely to have been insignificant compared to the increased risk due to her obesity and hypertension.

I have assumed that Mrs. Swartz's exposure to C8 was sufficient for her to qualify as a member of the *Leach* class, but her specific blood level (16.5 ng/ml) at the time it was measured (2006) was relatively low compared to the C8 blood levels of exposed individuals in Ohio and West Virginia based on the evaluation by Barry et al.(2013) and Vieira et al.(2013). Furthermore, as shown in the report by Mr. Washburn, her measured blood level is within the range of measurements that have been made in the general public in the United States, and elsewhere. The size of her tumor in March 2017 when it was excised was 2 cm. The estimated growth of renal cell carcinomas is in the range of approximately 0.5 cm. per year (Birnbaum et al., 1990; Bosniak et al., 1995; Oda et al., 2001; Zhang et al., 2009) indicating that her tumor first developed in approximately 2013.

The half-life of PFOA in human blood in community members is approximately 2.3 years (US EPA, 2016). In the seven years between her measured C8 blood level in March 2006 and the beginning of her tumor, there would have been approximately 3 half-lives of reduction in the C8 in her blood, so that by the 2013-2015 time frame her blood level would have been approximately 2 ng/ml, well within the background levels of the general public. Her amount of increased risk of developing kidney cancer from her C8 exposure would have been very small, and insignificant compared to her substantial amount of increased risk from her hypertension and her increased BMI.

I have also reviewed the expert opinion report of Dr. Vitaly Margulis. There are several statements in his report with which I disagree. He suggests that she might have had a history of hematuria for a long time, but that is inconsistent with both her medical records and the biology of her tumor. He intimates that her hip pain is related to her kidney cancer and her surgery, but that is highly unlikely given her history of significant arthritis and hip pain complaints pre-dating her kidney cancer. He also states that the amount of kidney removed was approximately one-third of the kidney. However, the pathology report indicates that the total amount of tissue removed was 4.3 grams. A normal kidney in a female adult is 115 to 155 grams, and since she had no evidence of renal disease other than the tumor and imaging studies indicated a normal sized kidney, even assuming the lower end of the normal range of kidney weight (115 grams), the amount of tissue removed at surgery amounts to less than 4% of a normal kidney. He suggests that she could develop adhesions, but given the type of surgery that is unlikely. Given the small size of the tumor and low grade, it is also unlikely that her tumor will recur. She is at increased risk of developing a second kidney tumor as is any patient with a kidney carcinoma. It is also unlikely that she had this carcinoma for the long period of time suggested by Dr. Margulis. My major disagreement with Dr. Margulis is his dismissal of obesity and hypertension as major causes of kidney cancer. This is not consistent with extensive literature on both issues as described above. Mrs. Swartz was clearly obese in her adult life, with a BMI reaching over 40 at times, which is defined as morbid obesity. Also, she is known to have had hypertension for several years and was being treated for it.

In summary, it is my opinion, based on a reasonable degree of medical and scientific certainty, that Mrs. Swartz, with her long history of obesity and hypertension and relatively low exposures to C8, would have developed her renal cell carcinoma even without her exposure to C8.

I reserve the right to revise or supplement these opinions if additional information becomes available.

A listing of the cases in which I have given testimony in the past 4 years is attached as Exhibit B.

For my services on this case, I am being compensated at the rate of \$600 per hour.